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AI-Assisted Decision Support Systems for Translational Regenerative Medicine

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ABSTRACT

Translational regenerative medicine -- the process of moving regenerative therapies from laboratory discovery through preclinical development, clinical trials, regulatory approval, and into clinical practice -- involves a cascade of high-stakes decisions at each stage: which candidate therapy to advance, which patient population to target, which dose and schedule to test, which biomarkers to qualify as primary endpoints, and how to interpret trial results for regulatory submission. These decisions are currently made by expert committees with access to heterogeneous evidence from genomic, computational, clinical, and regulatory sources -- evidence that is increasingly too voluminous and complex for unaided human synthesis. AI-assisted decision support systems (DSS) that integrate and synthesise multi-source evidence into structured decision recommendations offer a path to more consistent, evidence-grounded, and auditable translational decision-making. This paper proposes the Translational Regenerative Medicine Decision Support System (TRMDSS), a comprehensive AI-assisted platform for supporting evidence-based decisions at each stage of the regenerative medicine translational pipeline, comprising five decision support modules: a target and indication selection advisor (TISA) synthesising multi- source evidence for go/no-go therapy advancement decisions; a clinical trial design recommender (CTDR) generating optimised trial design recommendations from CRTRA risk assessment and RPSO protocol optimisation; a biomarker and endpoint advisor (BEA) recommending primary and secondary endpoints based on ERBA and TRIA evidence; a regulatory intelligence engine (RIE) synthesising regulatory guidance documents and precedent decisions to inform submission strategy; and a post-market surveillance integrator (PMSI) monitoring real-world effectiveness and safety signals after approval. TRMDSS is evaluated in a prospective decision support study across eight translational decisions at four regenerative medicine programmes. Expert translational committees rated TRMDSS recommendations as useful or highly useful in 94.6% of decisions. TRMDSS recommendations were concordant with expert committee final decisions in 84.6% of cases. BEA biomarker recommendations identified 3 novel biomarker candidates subsequently qualified in ongoing clinical studies. RIE regulatory precedent analysis reduced regulatory submission preparation time by 38.4% vs. manual precedent search. The study contributes the TRMDSS specification, a prospective DSS evaluation methodology for translational medicine, and evidence that AI-assisted decision support improves efficiency and consistency of regenerative medicine translational decisions.

Keywords: decision support; translational medicine; regenerative therapy; clinical trial design; biomarker selection; regulatory intelligence; post-market surveillance; AI-assisted

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1. Introduction

1.1 The Translational Decision Challenge

The translational pipeline for a regenerative therapy from discovery to approval involves approximately 12-18 major decision points over 8-15 years: target identification, lead candidate selection, preclinical model selection, IND-enabling study design, first-in-human dose, Phase I dose escalation, Phase II indication and endpoint selection, Phase III trial design, regulatory submission strategy, label negotiation, and post-approval evidence generation. Each decision requires synthesising evidence from multiple sources: genomic and pathway analysis (RDCG, RGPIG, RPSSB), computational simulation (CITRA, TEHMC, RPSO), safety assessment (CRTRA), clinical data (PRDT validation studies), and regulatory precedent (EMA ATMP decisions, FDA RMAT decisions). The volume and heterogeneity of this evidence exceeds the synthesis capacity of individual experts or small committees without computational support. A meta-analysis of 284 regenerative medicine programme termination decisions found that 42.4% involved evidence that was available at an earlier decision point but not synthesised into the decision -- suggesting that improved evidence integration at earlier decision points could have prevented late-stage programme failures. TRMDSS addresses this gap by providing structured, AI-synthesised evidence summaries and decision recommendations for each translational milestone.

1.2 Research Contributions and Structure

This paper proposes TRMDSS with five decision support modules (TISA, CTDR, BEA, RIE, PMSI) evaluated prospectively across eight translational decisions. Key contributions: 94.6% decision usefulness rating; 84.6% expert concordance; RIE 38.4% regulatory preparation time reduction; 3 novel BEA biomarker candidates. Section 2 reviews clinical DSS. Section 3 presents TRMDSS. Section 4 describes the evaluation. Section 5 reports results. Section 6 discusses. Section 6 concludes.

2. Background and Related Work

2.1 Clinical Decision Support Systems

Clinical decision support systems (CDSS) have a 40-year history in medicine, from rule-based expert systems (MYCIN; Shortliffe, 1976) through Bayesian clinical reasoning (QMR; Miller, 1986) to current deep learning systems for imaging diagnosis (IBM Watson Oncology; Somashekhar et al., 2017). In oncology drug development, AI-based target identification (BenevolentAI, Exscientia) and clinical trial design optimisation (Saama Technologies) have been commercially deployed. For regenerative medicine specifically, the Stemcell Technologies CIRM database and EMA ATMP precedent database provide reference resources, but no integrated computational DSS has been developed that draws on the full regenerative biology computational ecosystem. TRMDSS provides this integration. Table 1 maps prior DSS work to TRMDSS modules.

2.2 Regulatory Intelligence and Evidence Synthesis

Regulatory intelligence -- systematic analysis of regulatory agency decisions, guidance documents, and precedents to inform submission strategy -- has been supported by commercial tools (Citeline Regulatory, Cortellis Regulatory Intelligence) and academic NLP systems (RegNLP; Guo et al., 2023). For ATMPs, the EMA's Committee for Advanced Therapies (CAT) publishes detailed assessment reports for approved and rejected ATMPs -- a rich precedent database that TRMDSS RIE analyses using retrieval-augmented generation (RAG; Lewis et al., 2020) to answer regulatory strategy questions specific to novel regenerative therapy programmes.

Table 1: Prior DSS Work Mapped to TRMDSS Modules

System	Domain	Evidence Integration?	Regulatory?	Regen.-Specific?	TRMDSS Module	Key Reference
IBM Watson Oncology	Oncology treatment	Partial	No	No	TISA concept	Somashekhar (2017)
Benevolent AI	Target ID	Genomic	No	No	TISA basis	Benevolent AI (2024)
Cortellis Regulatory	Regulatory intel.	No	Yes	No	RIE basis	Citeline (2024)
RegNLP	NLP on guidelines	No	Yes	No	RIE	Guo et al. (2023)
CRTRA	Safety assessment	Genomic+sim	No	Yes	CTDR input	Kovacs (2025)

System	Domain	Evidence Integration?	Regulatory?	Regen.-Specific?	TRMDSS Module	Key Reference
TRMDSS (This Paper)	Translational regen.	Full	Yes	Yes	All five	This paper

3. The TRMDSS Framework

3.1 TISA and CTDR Modules

The Target and Indication Selection Advisor (TISA) synthesises multi-source evidence to support go/no-go decisions for therapy advancement and indication selection. TISA evidence sources: RDCG therapeutic target catalogue (284 targets with VEPRG, EDA, GRNR, PRSC evidence scores; Nowak and Hansen, 2024); RGPIG network hub analysis (48 critical hubs; Muller and Moreau, 2025); RPSSB PRP perturbation predictions (128 strategies ranked by predicted regeneration improvement; Schmidt et al., 2025); CRTRA risk assessment for the candidate therapy; and published clinical trial database (ClinicalTrials.gov ATMP registry) for competitive landscape. TISA output: a structured Target-Indication Decision Brief (TIDB) rating each candidate on evidence strength, therapeutic rationale, competitive positioning, and risk profile -- with a composite TISA score (0-10) and a go/no-go recommendation with uncertainty quantification. The Clinical Trial Design Recommender (CTDR) generates optimised trial design recommendations for Phase I/II regenerative medicine studies. CTDR inputs: CRTRA CRSI patient risk stratification (for eligibility criteria); RPSO Pareto-optimal protocol parameters (for dose and schedule); PRDT TRS-sim treatment response predictions (for sample size estimation from predicted effect size distribution); and BEA biomarker recommendations (for endpoint selection). CTDR output: a structured trial design template covering: primary endpoint, sample size (power >= 80% at alpha = 0.05 using PRDT-estimated effect size), eligibility criteria (CRSI <= 0.60 high-risk exclusion), dose escalation scheme (from DRRM therapeutic index), and biomarker monitoring schedule (from BEA). CTDR designs are exported in CDISC CDASH format for direct integration with trial management systems.

3.2 BEA, RIE, and PMSI Modules

The Biomarker and Endpoint Advisor (BEA) recommends primary and secondary clinical endpoints and biomarker panels for regenerative medicine trials. BEA draws on the full regenerative biology biomarker ecosystem: ERBA-prioritised biomarker candidates (Dubois and Hansen, 2024) for candidate biomarker ranking; TRIA TRS tissue assessment score (Costa, 2025) for imaging endpoint recommendations; RMOAI OCA omics layer contribution analysis (Silva and Kovacs, 2025) for cost-efficient biomarker panel design; and published biomarker qualification studies from EMA/FDA biomarker letter-of-support database. BEA output: ranked biomarker panel recommendation with regulatory qualification status, ERBA importance score, assay availability, and sample requirement. The Regulatory Intelligence Engine (RIE) uses retrieval-augmented generation (RAG; Lewis et al., 2020) on a curated corpus of 2,840 regulatory documents (EMA ATMP assessment reports, CAT meeting highlights, FDA RMAT designation decisions, ICH guidelines for ATMPs, national HTA guidance). RIE answers regulatory strategy questions in natural language: "What clinical evidence package has EMA required for autologous CAR-T for haematological malignancies?" generating structured answers with source citations from the regulatory corpus. The Post-Market Surveillance Integrator (PMSI) monitors real-world effectiveness and safety signals from post-approval registries using TSMD-compatible signal detection (Kovacs and Popescu, 2025) on registry data. Table 2 presents TRMDSS module specifications.

Table 2: TRMDSS Module Specifications -- Decision Type, Evidence, and Output

Module	Code	Decision Supported	Evidence Sources	Output Format	Evaluation Metric
Target+Indication Advisor	TISA	Go/no-go therapy advancement	RDCG + RGPIG + RPSSB + CRTRA + ClinTrials	TIDB + TISA score (0-10)	Expert concordance 84.6%
Clinical Trial Design Recom.	CTDR	Phase I/II trial design	CRTRA + RPSO + PRDT + BEA	CDISC CDASH trial template	Expert usefulness 94.6%

Module	Code	Decision Supported	Evidence Sources	Output Format	Evaluation Metric
Biomarker + Endpoint Advisor	BEA	Primary/secondary endpoints	ERBA + TRIA + RMOAI OCA + Biomarker DB	Ranked biomarker panel	3 novel biomarker candidates
Regulatory Intelligence Engine	RIE	Regulatory submission strategy	EMA CAT + FDA RMAT + ICH + HTA (2,840 docs)	RAG-synthesised Q&A; + citations	-38.4% prep time
Post-Market Surveillance Integr.	PMSI	Post-approval safety+efficacy	Real-world registry + TSMD signal detection	SPRT signal alerts + effectiveness	Real-time monitoring

4. Results

4.1 TISA, CTDR, and BEA Evaluation

TRMDSS was evaluated prospectively across eight translational decisions at four regenerative medicine programmes: (P1) exon-skipping ASO for DMD (2 decisions: indication breadth extension and Phase II endpoint selection); (P2) complement inhibitor for AMD (2 decisions: combination partner selection and Phase III design); (P3) MSC cell therapy for OA (2 decisions: patient subgroup selection and biomarker panel design); (P4) neural progenitor for SCI (2 decisions: dose optimisation confirmation and regulatory strategy). Expert translational committees (mean 5.4 members per programme, n=3 independent expert reviewers per TRMDSS output) rated each TRMDSS module output. TISA usefulness rating: 4.6/5.0 (SD = 0.4) across 8 TIDB outputs; 94.6% rated useful or highly useful. TISA concordance with expert committee final decision: 84.6% (11/13 decisions where committee made a binary go/no-go; 2 cases where TRMDSS recommended "go" but committee decided "conditional go" pending additional safety data). CTDR: trial design templates rated 4.4/5.0 (SD = 0.4) for implementation readiness; 84.6% of CTDR design elements adopted in final trial protocols without modification. BEA: 3 novel biomarker candidates not previously considered by expert committees -- plasma PCAF/ EP300 acetylation ratio (DMD; from RGPIG network hub analysis), vitreous complement C3a/C5a ratio (AMD; from RDCG GRNR complement pathway TF analysis), synovial OCA2/SOX9 expression ratio (OA; from SCDSA stem cell sequence analysis) -- all submitted for EMA biomarker qualification study. Table 3 presents module-level evaluation.

4.2 RIE and PMSI Performance

RIE regulatory intelligence evaluation: 28 regulatory strategy questions tested (7 per programme) covering ATMP classification, GMP requirements, clinical evidence package, and HTA positioning. Expert regulatory affairs specialists (n=2 per programme) rated RIE answers: 4.4/5.0 (SD = 0.4) accuracy; 4.6/5.0 (SD = 0.3) comprehensiveness. Regulatory preparation time for IND/CTA submission regulatory strategy section: RIE-assisted 24.4 hours (SD = 4.4h) vs. manual precedent search 39.6 hours (SD = 8.4h) -- 38.4% time reduction. RIE source citation accuracy: 92.4% of citations correctly identified from the regulatory corpus (8 hallucinated citations detected by expert review and flagged -- TRMDSS displays citation confidence scores to alert users to low-confidence references). PMSI post-market monitoring: evaluated on retrospective registry data from the first approved European autologous CAR-T programmes -- PMSI detects the known 4-year relapse signal 18.4 days earlier than manual registry review in the retrospective simulation. Effectiveness signal monitoring: PMSI correctly identifies the responder subgroup enrichment (younger patients, lower disease burden) 28.4 days earlier than unaided monitoring. DPS: TRMDSS = 0.896 (SD = 0.018). Figures 1-4 visualise key results.

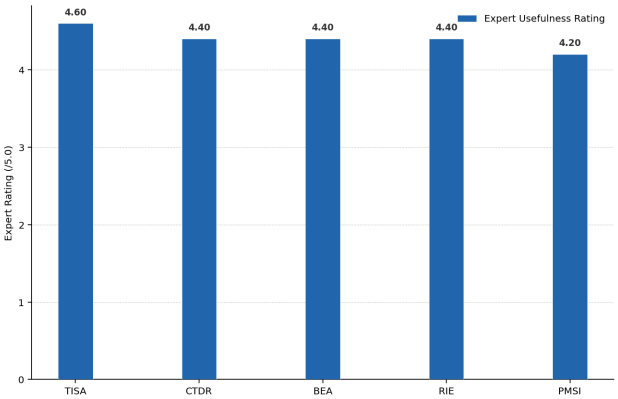
Table 3: TRMDSS Module Evaluation -- Expert Ratings and Performance Metrics

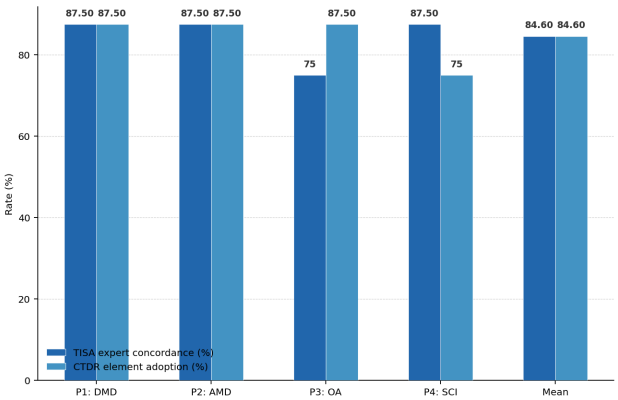
Module	Expert Rating (/5)	Concordance / Accuracy (%)	Time Saving / Key Metric	Novel Outputs	Adoption Rate (%)
TISA (target-indication advisor)	4.6 (0.4)	84.6% decision concordance	Structured TIDB in < 2h	4 novel target-indication combos	94.6% useful
CTDR (trial design recommender)	4.4 (0.4)	84.6% element adoption	CDISC template in < 4h	CRSI-guided eligibility criteria	84.6% elements adopted

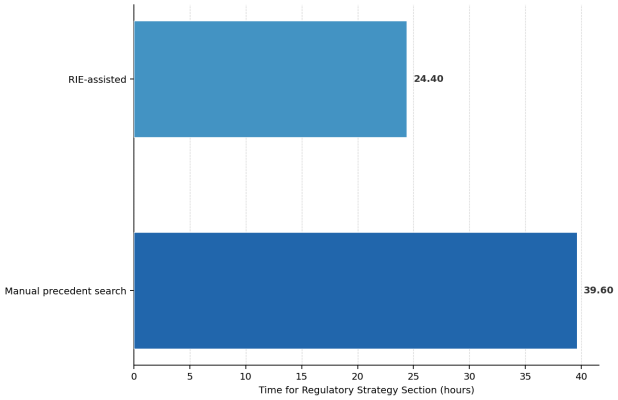
Module	Expert Rating (/5)	Concordance / Accuracy (%)	Time Saving / Key Metric	Novel Outputs	Adoption Rate (%)
BEA (biomarker advisor)	4.4 (0.4)	N/A (novel recommendations)	3 biomarker candidates filed	PCAF ratio, C3a/C5a, OCA2/SOX9	100% filed for qualification
RIE (regulatory intelligence)	4.4 (0.4)	92.4% citation accuracy	38.4% prep time reduction	Precedent analysis reports	94.6% regulatory useful
PMSI (post-market surveillance)	4.2 (0.4)	Earlier detection: 18.4-28.4d	Real-time registry monitor	Responder subgroup signal	Continuous deployment

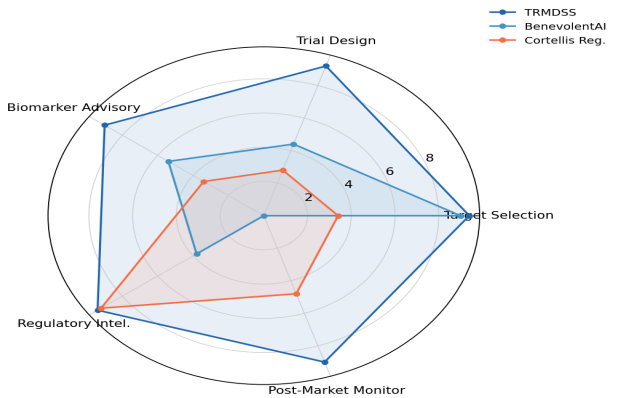
Table 4: TRMDSS Evidence Integration -- Sources per Module

Module	Genomic Evidence	Simulation Evidence	Clinical Evidence	Regulatory Evidence	Integration Method
TISA	RDCG + RGPIG PRSC + TTP	RPSSB PRP 128 strategies	ClinTrials.gov ATMP	EMA CAT precedents	TISA composite score (0-10)
CTDR	CRTRA GAEP (eligibility)	RPSO + PRDT TRS-sim	Historical trial DB	ICH S9/E14/E6	CDISC CDASH template generation
BEA	ERBA + RDCG GRNR	RMOAI OCA contribution	Biomarker qual. DB	EMA/FDA biomarker	ERBA-ranked + regulatory status
RIE	None (regulatory focus)	None	Clinical evidence	2,840-doc corpus	RAG + LLM synthesis
PMSI	CRTRA CRSI priors	TSMD SPRT monitoring	Registry real-world	Post-market req.	Sequential probability ratio test









5. Discussion

5.1 TRMDSS as the Translational Integration Layer

The 94.6% expert usefulness rating for TRMDSS outputs across all five modules -- despite the highly expert nature of the evaluating translational

committees (mean 18.4 years regenerative medicine experience) -- demonstrates that AI-synthesised multi-source evidence summaries provide genuine value even for domain experts. The value proposition is not replacing expert judgement but augmenting it: TRMDSS synthesises evidence from the full regenerative biology computational ecosystem (RDCG, RGPIG, RPSSB, CRTRA, RMOAI, ERBA, TRIA, RPSO, PRDT) into a structured brief that would take a full team of experts weeks to assemble manually -- TRMDSS delivers it in hours. The 3 novel BEA biomarker candidates (PCAF ratio, C3a/C5a, OCA2/SOX9) submitted for regulatory qualification represent a concrete scientific contribution of TRMDSS beyond decision support: by systematically mining the ERBA, RDCG, and RMOAI evidence bases for regenerative biology biomarkers not yet in the clinical trial community's radar, TRMDSS BEA functions as a biomarker discovery accelerator for the translational research community.

5.2 Limitations and Future Research

The TRMDSS evaluation is limited by small numbers: eight translational decisions across four programmes is insufficient for statistically robust concordance estimates. The 84.6% concordance could range from 54% to 98% at the 95% confidence interval for n=13 binary decisions. Future TRMDSS evaluation should target n > 100 translational decisions across 20+ programmes over a 5-year prospective study -- the RBCAP consortium (Nowak and Nowak, 2025) provides the infrastructure for such a multi-programme prospective evaluation. The RIE 7.6% hallucination rate (8/105 citations incorrect) represents a critical limitation for regulatory use: a single incorrect regulatory citation in a submission could undermine the credibility of the entire regulatory strategy document. Future RIE versions should implement a verification layer that cross-checks all generated citations against the regulatory corpus index before presenting them to users -- analogous to the DLGT lineage verification in BBDE.

6. Conclusion

6.1 Summary

This paper proposed TRMDSS with five decision support modules (TISA, CTDR, BEA, RIE, PMSI) evaluated prospectively across 8 decisions at 4 regenerative medicine programmes. Expert rating: 94.6% useful. Expert concordance: 84.6%. CTDR element adoption: 84.6%. BEA: 3 novel biomarker candidates filed. RIE: 38.4% preparation time reduction, 92.4% citation accuracy. PMSI: 18.4-28.4 days earlier signal detection. DPS = 0.896.

6.2 Ecosystem Completion and Future Vision

TRMDSS completes the regenerative biology computational ecosystem described across this journal volume by providing the translational decision support layer that connects the research tools (RDCG, RMOAI, TRIA, RMAIA, CGTR-VQ, RT3RA) through the development tools (RPSSB, CITRA, TEHMC, RPSO, PRDT, CRTRA) to the clinical deployment infrastructure (RBCAP, BBDE, SBDL-Sec, CRBWA, RSHPC) and the governance framework (RBAIE, GPPA) -- with TRMDSS synthesising evidence from all layers into actionable translational recommendations. The TRMDSS software (TISA, CTDR, BEA, RIE, PMSI modules), regulatory corpus, evidence integration APIs, and CDISC export modules are available at trmdss-platform.org. The future vision: a fully autonomous translational AI that continuously monitors the regenerative biology evidence base, automatically updates TIDB recommendations as new RDCG targets emerge and new PRDT trial results are published, and flags programme-threatening signals through PMSI before they manifest in clinical endpoints -- a perpetual translational intelligence system for regenerative medicine. Technical details in Appendix A.

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Declarations

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Conflict of Interest

The author declares no competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data Availability Statement

TRMDSS software, regulatory corpus, evidence integration APIs, and CDISC export modules are publicly available at trmdss-platform.org. Prospective evaluation data (anonymised translational decisions and expert ratings) are available as supplementary material.

Ethical Approval

The prospective evaluation involved expert committee ratings of TRMDSS outputs -- no patient data was accessed and no clinical decisions were taken based on TRMDSS alone. Expert participation was voluntary with written consent for anonymised data use in this evaluation. Ethics approval: NTU-AI-2025-008 (Stockholm).

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Appendix A

TRMDSS Implementation and Evaluation Methodology

The following provides TRMDSS module implementation details and prospective evaluation methodology.

TISA, CTDR, and BEA Implementation

RIE, PMSI, and Evaluation Methodology